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Petersen et al.

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(45) **Date of Patent: *May 3, 2005**

(54) **METHOD FOR THE PREPARATION OF 5-CARBOXYPHTHALIDE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/140,361**

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(65) **Prior Publication Data**

US 2002/0165403 A1 Nov. 7, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/690,301, filed on Oct. 17, 2000, now Pat. No. 6,458,973.

(30) **Foreign Application Priority Data**

Nov. 1, 1999 (DK) 1999 01569

(51) **Int. Cl.**[7] **C07D 307/77**

(52) **U.S. Cl.** **549/305**

(58) **Field of Search** 549/305, 467

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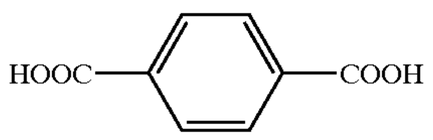
(57) **ABSTRACT**

5-carboxyphthalide is obtained with very high purity and in high yields by a convenient process comprising reaction of terephthalic acid



with paraformaldehyde $HO(CH_2)_nH$ in oleum.

16 Claims, No Drawings

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METHOD FOR THE PREPARATION OF 5-CARBOXYPHTHALIDE

CROSS REFERENCE TO RELATED APPLICATION

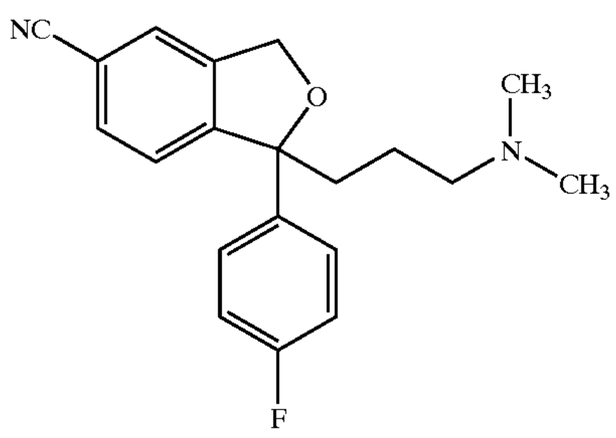
This application is a continuation of U.S. patent application Ser. No. 09/690,301, filed Oct. 17, 2000 now U.S. Pat. No. 6,458,973.

The present invention relates to a novel process for the preparation of 5-carboxyphthalide, a starting material for the manufacture of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

BACKGROUND OF THE INVENTION

Citalopram is a selective serotonin reuptake inhibitor which has successfully been marketed as an antidepressant drug for some years. It has the following structure:

Formula I



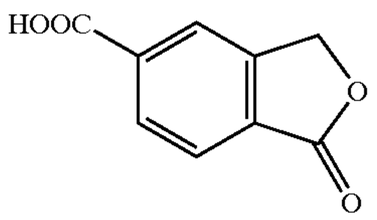
and it may be prepared by the process described in U.S. Pat. No. 4,650,884 according to which 5-cyanophthalide is subjected to two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively, and the resulting dicarbinol compound is subjected to a ring closure reaction by dehydration. The 5-cyanophthalide may in its turn be obtained by reaction of 5-carboxyphthalide with a dehydrating agent and a sulfonamide of the formula $H_2N—SO_2—R$ wherein R is NH_2, alkyloxy, optionally substituted phenyloxy, or substituted phenyl in order to obtain 5-cyanophthalide, cf. our co-pending Danish patent application No. PA199801718.

5-Carboxyphthalide has been described as a useful intermediate in the polymer and paint industry. However, no reliable commercial source is available at present. A known process comprises catalytic hydrogenation of trimellithic acid (DE-A1 2630927). This process provides a mixture of the 5- and 6-carboxyphthalides and, accordingly, it requires elaborate and costly purification. According to J. Org. Chem. 1970, 35, p. 1695-1696, 5-carboxyphthalide is synthesised by reaction of terephthialic acid with trioxanie in liquid SO_3. During this process, trioxane sublimates and precipitates thereby obstructing the equipment.

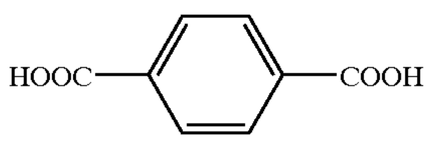
Though a number of other methods failed, it has now been found that 5-carboxyphthalide may be prepared from terephthalic acid in high yields by a convenient, cost-effective procedure.

DESCRIPTION OF THE INVENTION

Accordingly, the present invention provides a process for the manufacture of 5-carboxyphthalide



comprising reaction of terephthalic acid



with paraformaldehyde, $HO(CH_2O)_nH$, in oleum.

By the process of the invention, 5-carboxyphtlialide is obtained with very high purity and in high yields (>about 75%). Furthermore, as compared with the prior art process (J. Org. Chem. 1970, 35, p. 1695-1696), the process of the invention takes place without precipitation of sublimated trioxane which obstructs the equipment e.g. by precipitating in condensers.

The oleum used is commercially available oleum. So the following are available from Aldrich/Fluka:

12–17% SO_3 (Fuming sulfuric acid) 15% oleum
18–24% SO_3 (Fuming sulfuric acid) 20% oleum
27–33% SO_3 (Fuming sulfuric acid) 30% oleum

From other sources 20% oleum contains 20–25% SO_3

In the method of the invention, the terephthalic acid is condensed with paraformaldehyde liberating water, which reacts with the SO_3. When the reaction is complete, 5-carboxyphthalide may be isolated as follows. The reaction mixture is hydrolysed with water. The condensed product, 5-carboxyphthalide inclusive possible diphthalide impurities may then be filtered off, and the 5-carboxyphthalide may be dissolved in aqueous medium by adjusting pH to about 6.7 to 7.3, leaving possible diphthalide impurities in the solid phase The diphthalide present may be filtered off whereupon 5-carboxyphthalide may be precipitated by acidification, filtered off, washed with water and dried.

Preferably 1.0–1.33 equivalents CH_2O and 1.0–2.5, preferably 1.0–2.0 are used. More preferably 1.25–1.5 equivalents SO_3 per equivalent terephthalic acid are used. Most preferably, about 1.37 equivalents (corresponding to about 33 kg 20–25% oleum/kg terephthalic acid) are used per equivalent terephthalic acid.

The reaction of terephthalic acid with paraformaldehyde is carried out at elevated temperature, conveniently at about 50–148° C., preferably 115–125° C. or 138–148° C. The reaction time is not critical and may easily be determined by a person skilled in the art, a reaction time of 17–21 hours is preferably used for a 210 kg batch at 115–125° C. The time is decreased with increasing temperature.

The adjustment of pH to 6.3 to 7.3 in order to dissolve the 5-carboxyphthalide formed may be effected by NaOH, e.g. about 10% aqueous NaOH.

Acidification in order to precipitate the 5-carboxyphthalide may be carried out by adding sulphuric acid until pH=2.

The terephthalic acid used as a starting material is commercially available.

EXAMPLES

The invention is father illustrated by the following example.

Example 1

5-Carboxyphthalid

Terephthalic acid (10 kg) is charged into a reactor. Oleum (20% (18–24% SO_3); 6 kg/kg terephthalic acid) is added and then paraformaldehyde (1.33 equivalents, 0.24 kg/kg terephthalic acid) is added. The mixture is agitated at 125° C. for 17 hours. Water (13 kg/kg terephthalic acid and filter aid is added, the temperature is adjusted to about 70° C. The precipitate is filtered of, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with NaOH, activated carbon, 0.07 kg/kg terephthalic acid is added, and then the mixture is filtered, the precipitate is rinsed with water. The temperature of the filtrate is adjusted to about 65° C. and the pH is adjusted to about 2 with 50% sulfuric acid. The 5-carboxyphthalide precipitated is separated by filtration washed and dried. Yield 83%.

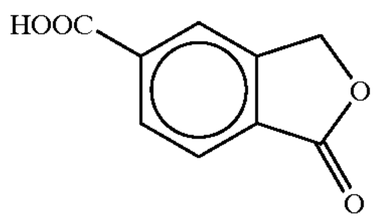
Example 2

5-Carboxyphthalid

Oleum (20–25% SO_3 43 kg) is charged into a reactor. Terephthalic acid (13 Kg) and then paraformaldehyde (3.8 Kg) is added. The mixture is agitated at 138–148° C. for 4½ hours. Water (87 L) is added and the temperature is adjusted to about 100° C. The precipitate is filtered of, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with NaOH (about 10%), activated carbon, 0.5 Kg is added, and then the mixture is filtered, the precipitate is rinsed with water. The temperature of the filtrate is adjusted to about 85° C. and the pH is adjusted to about 2 with 96% sulfuric acid. The 5-carboxyphthalide precipitated is separated by filtration washed and dried. Yield 82%.

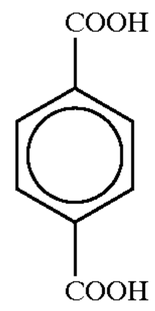
What is claimed is:

1. A process for the preparation of 5-carboxyphthalide of formula A



(A)

which comprises forming a mixture by adding formaldehyde and terephthalic acid of formula I



(I)

to fuming sulfuric acid containing at least 18% of SO_3, heating the mixture at 50–148° C. and isolating the 5-carboxyphthalide thus obtained.

2. A process according to claim **1**, in which the mixture is heated at 138–148° C.

3. A process according to claim **1**, in which the mixture is heated at 115–125° C.

4. A process according to claim **1**, in which the fuming sulfuric acid contains 18–24% S_3.

5. A process according to claim **1**, in which the fuming sulfuric acid contains 20–25% SO_3.

6. A process according to claim **1**, in which the fuming sulfuric acid contains 27–33% SO_3.

7. A process according to claim **1**, in which formaldehyde is used in form of its precursor paraformaldehyde.

8. A process according to claim **1**, in which 5-carboxyphthalide is isolated by neutralization of the reaction mixture with a base.

9. A process according to claim **8**, in which said base is an alkaline metal base.

10. A process according to claim **9**, in which said alkaline metal base is sodium hydroxide.

11. A process according to claim **1**, in which formaldehyde is added to fuming sulfuric acid after the addition of terephthalic acid.

12. A process according to claim **1**, in which, at the end of the reaction, the 5-carboxyphthalide is isolated by the formation of a solution containing a salt thereof which is neutralized with an acid.

13. A process according to claim **12**, in which said salt is the sodium salt.

14. A process for the synthesis of citalopram, in which a process for the synthesis of 5-carboxyphthalide according to claim **1** is contained.

15. Citalopram which has been produced by a process comprising the process for the synthesis of 5-carboxyphthalide according to claim **1**.

16. A process according to claim **1**, in which the fuming sulfuric acid contains at least 20% SO_3.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,888,009 B2
DATED : May 3, 2005
INVENTOR(S) : Hans Petersen et al.

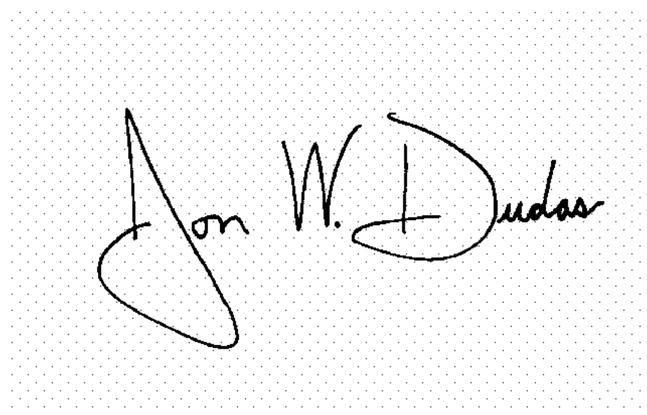
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,

Item [63], **Related U.S. Application Data**, please delete "Continuation of application No. 09/690,301, filed on Oct. 17, 2000, now Pat. No. 6,458,973." and substitute with -- This is a division, of application Serial No. 09/692,653, filed October 19, 2000 now Pat. No. 6,403,813 --.

Signed and Sealed this

Second Day of August, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office